

Case Report

Fenofibrate-induced Acute Cholestatic Hepatitis

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Key Words

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Fenofibrate-induced acute or chronic hepatitis is rare, and only 11 reports from French, Italian or Spanish literature have been published up to date. We report a case of fenofibrate-induced acute cholestatic hepatitis. To the best of our knowledge, this is the first one reported in Taiwan. A 61-year-old man developed acute cholestatic hepatitis after taking fenofibrate 100 mg tid for 10 days. Laboratory profile on admission showed serum total bilirubin 9.3 mg/dL, direct bilirubin 2.7 mg/dL, alanine aminotransferase 249 IU/L, aspartate aminotransferase 259 IU/L, alkaline phosphatase 259 IU/L, and gamma-glutamyl transpeptidase 1014 IU/L. Pathology proved hepatocanicular cholestasis in liver. Fenofibrate was discontinued immediately. His clinical manifestations and liver function tests improved gradually and returned to nearly normal in 2 months. We suggest that liver function tests, including total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transpeptidase, be checked at least 2 weeks after taking the drug and that serum aminotransferase be monitored every 3 months during the first 12 months of therapy. Treatment should be discontinued if alanine aminotransferase values increase by more than 100 IU/L.

Fenofibrate is a synthetic phenoxy-isobutyric acid derivative first synthesized in 1975. It reduces serum triglyceride, total cholesterol and LDL-C, and raises HDL-C.¹ The standard formulation of fenofibrate (200 to 400 mg daily) has demonstrated beneficial lipid-modifying effects in patients with type IIa, IIb and IV primary dyslipidemia and in the less commonly diagnosed forms, type III or V dyslipidemia.² Although asymptomatic elevations in serum transaminase in excess of threefold above the upper limit of normal have been reported to occur in 6.3% of patients taking fenofibrate at doses of 200-300 mg/day, morphologic studies have not revealed significant differences in the results of light microscopy and electron microscopy testing between hyperlipidemic nondrug controls and fenofibrate recipients.¹

Recently, autoimmune hepatitis induced by fibrates has been reported.³ A few cases of acute hepatitis and chronic hepatitis induced by fenofibrate have been also reported.³⁻¹³ Here we report a case of fenofibrate-in-

duced acute cholestatic hepatitis in Taiwan.

CASE REPORT

A 61-year-old man was admitted on July 22, 2000 due to yellowish skin discoloration and tea-colored urine for 12 days. He had had the history of diabetes mellitus, hyperlipidemia and hypertension for more than 10 years and had been regularly followed up at our Metabolic clinic with drugs of aspirin, glibenclamide, metformin, paravastin, nifedipine and dipyridamole for several years. Fenofibrate 100 mg tid was prescribed due to hyperlipidemia 26 days prior to the admission. Progressive yellowish skin discoloration and tea-colored urine developed since 2 weeks before admission. Body weight loss 3 kg was also found in recent 2 weeks.

The patient had never received blood transfusion and denied the use of alcohol or intravenous drugs. No

specific family history of liver disease was reported. There was no history of environmental exposure to hepatotoxins. Serum aminotransferase and bilirubin were normal before the development of liver disease. Physical examination revealed icteric sclera and yellowish skin discoloration. There was no splenomegaly, ascites, spider angioma, palmar erythema or peripheral edema.

Laboratory profile on admission showed serum total bilirubin (TB) 9.3 mg/dL (reference range: 0.2-1.6 mg/dL), direct bilirubin (DB) 2.7 mg/dL (0-0.3 mg/dL), alanine aminotransferase (ALT) 249 IU/L (0-40 IU/L), aspartate aminotransferase (AST) 243 IU/L (5-45 IU/L), alkaline phosphatase (ALK-P) 259 IU/L (10-100 IU/L), gamma-glutamyl transpeptidase (GGT) 1014 IU/L (4-61 IU/L), albumin 4.0 gm/dL (3.7-5.3 gm/dL), prothrombin time 11.6 seconds (control 11.4 seconds). Series of examinations and results were as follows: anti-HAV IgM (-), HBsAg (-), anti-HBc IgM (-), anti-HCV EIA (-), plasma hemoglobin: 2.8 mg/dL (1-5 mg/dL), urine hemosiderine (-), direct and indirect Coombs' test (-), haptoglobin: 38.3 mg/dL (30-200 mg/dL), reticulocyte: 1.51%, IgE: 208 IU/mL (reference range: < 200 IU/mL), total eosinophil counts: 150/mm³ (100-300/mm³). Antibodies to mitochondria, smooth muscle cell and nuclei were absent. Abdominal sonography did not show evidence of liver cirrhosis. Endoscopic retrograde pancreatocolangiography showed normal gallbladder and no dilatation of biliary tract.

A percutaneous liver biopsy was performed. Histologic examination showed normal lobular architecture, spotted necrosis and cholestasis in liver lobules, mild

chronic inflammation and fibrosis in portal area, mild fatty change and bile duct degeneration.

Fenofibrate was discontinued due to the suspected etiology of acute hepatitis. The patient was treated with ursodeoxycholic acid 600 mg qd. His clinical manifestations and liver function tests improved gradually. He was discharged on August 5, 2000. Two months later, on follow-up, the liver function tests nearly returned to normal. The levels of total bilirubin, ALT, AST, GGT, ALK-P are showed in Fig. 1.

DISCUSSION

The liver injury affecting our patient can be ascribed to fenofibrate because: 1) there was no history of liver or biliary tract disease and the patient had documented normal liver enzymes before fenofibrate administration; 2) there was no alcohol abuse and no serological or circumstantial evidence for viral hepatitis; 3) tests for serum antitissue antibodies were negative; 4) obstruction of the common bile duct and sclerosing cholangitis were eliminated by endoscopic retrograde pancreatocolangiography; 5) hepatocanicular cholestasis was with mild inflammatory response and the interlobular biliary tracts were intact. The temporary evolution also implicated fenofibrate as an offending drug, as its withdrawal was followed by permanent improvement of laboratory findings.

Adverse events attributable to standard fenofibrate have been reported to occur with an overall incidence of approximately 6% in short-term studies, with gastrointestinal disturbance occurring most frequently. Only a small increase in incidence of elevated levels of serum aspartate aminotransferase and alanine aminotransferase were reported.¹ Fenofibrate-induced acute or chronic hepatitis is a rare side effect and only 11 reports have been published in French, Italian or Spanish literature up to date.³⁻¹³ To the best of our knowledge, there was no similar case report in Taiwan.

Pierre-Henri *et al.* revealed fenofibrate-induced chronic active hepatitis with presence of antinuclear antibodies.⁵ Rigal *et al.* reported a case of fenofibrate-induced severe mixed hepatitis.¹⁰ Ganne-Carrie *et al.* have reported chronic liver disease resembling type 1 autoimmune chronic hepatitis (case numbers, 5) with increased serum

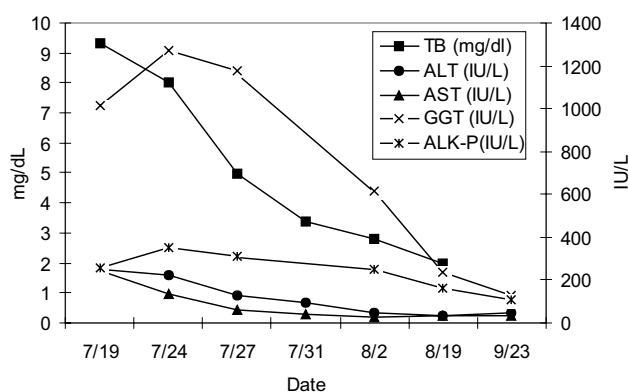


Fig. 1. The changing profile of liver function tests. TB = total bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALK-P = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase.

aminotransferase activity, hypergammaglobulinemia and high titers of anti-nuclear antibodies induced by fibrate.³ After discontinuation of fibrate, aminotransferase activity normalized within 6 weeks either spontaneously or under immunosuppressive therapy. One case of chronic intra-hepatic cholestasis after 5-month treatment of fenofibrate has been reported.⁶ GGT activity remained moderately increased 2 years after discontinuation of treatment. Cholestasis is interference with bile flow or formation with clinically raised serum alkaline phosphatase and gamma-glutamyl transpeptidase. In this case, marked elevation of GGT activity, associated with a moderate increase in alkaline phosphatase and aminotransferase activities, which was comparable with cholestatic hepatitis, occurred after fenofibrate (100 mg) 1# tid was prescribed for 2 weeks. The clinical manifestations and the laboratory evaluation of this patient excluded the possibility of hemolysis, ineffective erythropoiesis and other congenital liver disease although the initial ratio of direct bilirubin to total bilirubin was about 30%. The marked elevation of GGT activity in our case is similar to other reported cases.

After withdrawal of this drug and use of ursodeoxycholic acid 600 mg per day, liver functional test returned to normal after more than 1 month. Ursodeoxycholic acid was prescribed according to its effect in treating primary biliary cirrhosis. The drug may have cytoprotective and choleric effects and alter the bile pool by competition for uptake by ileal bile acid receptors.¹⁴ Whether it can shorten the course of the disease is unknown.

This case emphasizes that fenofibrate can induce cholestatic hepatitis. It is thus needed to monitor liver function tests in patients receiving fenofibrate therapy. Adkins *et al.* recommend regular monitoring of serum transaminase every 3 months during the first 12 months of therapy with fenofibrate. Treatment should be discontinued if ALT values exceed 100 IU/L.² We suggest the liver function tests, including ALT, AST, GGT, ALK-P and TB, be followed up at least 2 weeks after taking the drugs.

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